



Application No.: 08/737,633

Docket No.: I0717.0003/0US0

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Fabrizio Samaritani, et al.

Application No.: 08/737,633

Group Art Unit: 1647

Filed: November 15, 1996

Examiner: R. Landsman

For: IFN BETA LIQUID FORMULATIONS

DECLARATION

I, Mark C. Manning, declare that

1. A copy of my Curriculum Vitae is attached hereto.
2. I have reviewed the entire file of the-above application in connection with this declaration.
3. I understand that what is being claimed is a liquid pharmaceutical composition which contains only from about 0.6 to 24 MIU/ml of interferon-beta, mannitol, an acetate buffer at a pH between 3.0 and 4.0 and, optionally, albumin; a process for making such a composition; and a hermetically sealed container in sterile conditions containing the liquid pharmaceutical composition. I further understand that the examiner has determined that when there is one MIU/ml interferon-beta, 54.6 mg/ml of mannitol, 0.5 mg/ml of albumin in a solution of 0.01 M acetate buffer at pH 3.5, the invention is both novel and unobvious.
4. I understand that claims in this application have been rejected as being obvious over a combination of Hanisch (U.S. Patent 5,643,566) in view of Hershenson (U.S. Patent

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5,004,605), possibly combined with Cymbalista (U.S. Patent 4,647,454). I disagree with the assertion that the claimed invention is obvious over these references for the following reasons.

5. The Hanisch patent relates to purifying and processing recombinant human interferon-beta or interleukin-2, in order to realize a composition in which in such recombinant protein is dissolved in a non-toxic, therapeutically compatible aqueous-based carrier at a pH ranging from 6.8-7.5. The procedures described are designed to avoid extreme alkaline conditions. In one procedure, the recombinant protein is the desalted at a pH of about 8.5-10 and the pH of the desalted product adjusted to about 2-4, preferably 3-4, in order to precipitate the transfer component from the solution, which is then removed, and the pH is eventually raised to 6.8-7.5. Hanisch indicates that the low pH solution does not require a stabilizer at column 5, lines 16-19. As a result, the low pH solution can be maintained as a liquid or can be lyophilized and when lyophilized, a carbohydrate stabilizer such as dextrose or mannitol can be added (column 5, lines 20-23).

6. Hanisch makes claims (e.g., claims 2, 7, 17 and 19) for lyophilized formulations and not liquid formulations. It is well known that carbohydrates and polyols stabilize proteins in a liquid or lyophilized formulation by vastly different mechanisms. In a lyophilized preparation, the carbohydrates serve to replace the water removed by freeze-drying. In a liquid formulation, as claimed in Samaritani, the stabilization comes from acting as an excluded solute, thereby increasing the thermodynamic stability of the protein in solution. Hanisch does not teach such stabilization of a liquid formulation. This is a critical distinction.

7. Hanisch then teaches that the final stable pharmaceutical composition is the recombinant protein dissolved in a non-toxic, inert, therapeutically compatible aqueous-based

9. I note that, in the most recent Office Action, it is asserted that even though Hanisch does not teach the use of a buffer in a pharmaceutical composition, those skilled in the art would immediately envision the use of a buffer in a preparation of a pharmaceutical composition and it would be obvious to use a buffer in order to maintain the pH of the solution, especially if the pharmaceutical composition was to be stored. I find nothing in Hanisch which suggests that there is a problem in maintaining the pH of the solution without the presence of a buffer. Proteins are polyelectrolytes that can buffer solutions themselves. Moreover, at low concentrations, they may be unable to alter the pH of the solution significantly. In either case, a buffer is not necessarily needed, despite the assertions of the examiner. Moreover, given the large changes in pH during processing described in Hanisch, the choice of a single buffer would

be problematic and the teaching would have had to include specifications for buffer exchange, if the invention was to be practiced.

10. I understand that the Hershenson patent has been relied on to show the amount of interferon-beta. I understand that this patent has also been cited to show the use of a pH 2-4 buffer, and while it does so, incorporating the use of such a buffer in the Hanisch procedure is contraindicated of the reasons already stated.

11. The Hershenson patent indicates that the buffers described can be phosphoric acid, glycine and citric acid and more preferably, phosphate (column 9, lines 16-20). Acetate buffers are not disclosed.

12. Hershenson refers to a buffer-containing composition, which also contains what is referred to as a "stabilizer/solubilizer", which is either glycerol or certain polyethylene glycol polymers. First, there is no data to support the fact that these compounds are "solubilizers". In fact, it is well known that excluded solutes, like glycerol and PEG, increase the chemical potential of the native state, which would lower, not raise, the solubility. Certainly, there is no data in the literature to suggest that mannitol is a solubilizer of interferon. Second, Hershenson teaches that either PEG or glycerol is required for proper stabilization, with no mention of mannitol or albumin.

13. Even if one were to ignore the clear reasons not to employ a buffer in the Hanisch composition and employed a Hershenson buffer in the Hanisch composition, one would also employ either glycerol or the polyethylene glycol polymers as a stabilizer. The resulting composition would not be the composition claimed in the above-identified application, even ignoring the fact that there is no teaching of acetate buffer in either Hanisch or Hershenson.

14. I note that the Office Action states that Hershenson does not teach that glycerol or polyethylene glycol polymers are required. I disagree and believe that Hershenson does teach this. These stabilizers are included in every buffered composition described. Furthermore, the Hanisch patent does not contain a buffer in any of the final liquid formulations. Hershenson does not teach any lyophilized formulations. Therefore, even in combination, these two do not teach a low pH, liquid formulation containing buffer, mannitol and, possibly, albumin, as claimed in the current patent application. Taken together, they teach a buffered composition containing glycerol or a polyethylene glycol.

15. I understand the Cymbalista patent has been cited to show a connection between an acetate buffer and interferon-beta. The patent does teach a stable composition containing interferon-beta, conventional excipients, a buffer and PVP as a stabilizer. However, I see nothing in this reference that indicates that the PVP can be eliminated. In fact, all of the data in the patent indicates that PVP is not only essential but superior to other 'conventional' stabilizers. There is nothing in Cymbalist which shows that the acetate buffer would give any degree of stabilization in the absence of PVP. Moreover, the use of a buffer *per se* is contrary to Hanisch, as discussed earlier.

16. Given the prior art listed by the examiner, I see no evidence of obviousness of a stable, buffered liquid formulation of interferon-beta at low pH using mannitol and possibly albumin as stabilizers. Furthermore, I believe that the data in the application shows that the claimed combination gives surprising and unexpected results. Table 1 shows a formulation of interferon-beta in a citrate buffer at pH 3 losing 27% of its potency after day 1 and virtually all

17. The data shown in Table 5 should be taken into consideration. It shows that the formulation covered by the claims (ACE/MAN/3.5) does not decrease in its concentration of active ingredient (interferon-beta), even after storage at 25° C for 9 months! Nothing in the prior art teaches that the combination of the interferon-beta, mannitol and an acetate buffer at a pH between 3.0 and 4.0, and optionally albumin, will give such outstanding results. The outstanding results here are surprising and unexpected.


19. I declare that all statements made herein of my own knowledge are true and that all statements made on the information and belief are believed to be true and further that these

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statements were made with the knowledge that willful false statements or the likes are made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the U.S. Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date: SEPT. 26, 2003

By: 
Name: 

CURRICULUM VITAE

Mark C. Manning, Ph.D.

I. GENERAL INFORMATION

Home Address: 4968 Valley Oak Drive
Loveland, CO 80538

Home Telephone: 970-663-6006

Office Address: School of Pharmacy, Room 227
Campus Box C238
University of Colorado Health
Sciences Center
Denver, CO 80262

Office Telephone: 303-315-6162
Office Fax: 303-315-6281

II. EDUCATION

YEAR	INSTITUTION	DEGREE CONFERRED
1978	Hope College	A.B., Chemistry
1979	Northwestern University	M.S., Chemistry
1983	Northwestern University	Ph.D., Inorganic Chemistry

III. PROFESSIONAL EXPERIENCES

YEAR	TITLE	INSTITUTION
1978-1982	Graduate Student	Northwestern University (Dept. of Chemistry)
1982-1984	Postdoctoral Associate	Colorado State University (Dept. of Chemistry)
1984-1988	Postdoctoral Associate	Colorado State University (Dept. of Biochemistry)

IV. ACADEMIC APPOINTMENTS

YEAR	TITLE	INSTITUTION
1988-1990	Assistant Professor of Pharmaceutical Chemistry	University of Kansas
1989-1990	Courtesy Assistant Professor of Biochemistry	University of Kansas
1990-1997	Assistant Professor of Pharmaceutics	University of Colorado Health Sciences Center
1997-present	Associate Professor of Pharmaceutics	University of Colorado Health Sciences Center
2001-present	Affiliate Faculty	Colorado State University Veterinary Teaching Hospital
2002-present	Head, Pharmacology Laboratory Animal Cancer Center	Colorado State University Veterinary Teaching Hospital

V. CONSULTING ACTIVITIES

Scientific Advisory Boards:

RxKinetix, Inc., Louisville, CO, Co-Founder, 1996. Co-Chair, Medical and Scientific Advisory Board, 1997-1999, 2001-present
Imutec Corporation (now Lorus Pharmaceuticals), Scarborough, Ontario, Member, Medical and Scientific Advisory Board, 1995-1997
HTD Biosystems, Hercules, CA, Co-Founder/Chief Technical Officer, 2001-present

Consultant for:

Alan Laufman, J.D., M.D., Dallas, TX, 1994
Alza Corporation, Palo Alto, CA, 1994-1995; 1998-2000; 2002
Amen, Thousand Oaks, CA, 2003
Antigenics, Woburn, MA, 2002
AntiVirals, Inc., Portland, OR, 1997
Athena Neurosciences/Elan Pharmaceuticals, S. San Francisco, CA, 1998-2000
Atrix Laboratories, Fort Collins, CO, 1992-1994; 1998-1999
Baxter Healthcare, Round Lake, IL, 1998
Baxter Hyland, Fremont, CA, 1998
Bayer (formerly Miles) Biotechnology, Inc., Berkeley, CA, 1995-2001
Bayer Pharmaceutical Division, Clayton, NC, 1997
Bristol-Myers Squibb, New Brunswick, NJ, 1996-1997
Cell Therapeutics, Seattle, WA, 2002
Clifford Chance, New York, NY, 2000-2001
Cytel Corporation, San Diego, CA, 1995
Elan Pharmaceuticals, S. San Francisco, CA, 1999-2000
G.D. Searle/Monsanto, Skokie, IL, 1998-1999
ICOS, Bothell, WA, 2001-2002
IntraBiotics, Mountain View, CA, 1999
Millipore Corporation, Bedford, MA, 1997-1998
Montgomery, Little and McGrew, Attorneys at Law, Englewood, CO, 1996
NaPro Biotherapeutics, Boulder, CO, 1992-1995
Novartis Pharmaceuticals, Summit, NJ, 2002
Neurobiological Technologies, Inc., Richmond, CA, 1995-1997
Oread Laboratories, Lawrence, KS, 1990
Patzner Consulting, Portola Valley, CA, 2002
R.W. Johnson Research Institute, Raritan, NJ, 1997-1998
Roche Pharmaceuticals, Nutley, NJ, 2002
Somatogen, Boulder, CO, 1994
SP Pharmaceuticals, LLC, Albuquerque, NM, 2000
Trimeris, Inc., Durham, NC, 1996

VI. TEACHING ACTIVITY

YR.	COURSE		SEMESTER CREDITS	NO. OF STUDENTS	CONTACT HRS.
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Colorado State University

1987	CHEM 261	Inorganic Chemistry	3	25	48 lecture
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University of Kansas

1988	PHCH 631	Pharmaceutics Lab II	1	80	64 laboratory
1988	CHEM 959	Bioanalytical Chemistry	3	15	3 lecture
1989	PHCH 624	Pharmaceutics II	3	80	6 lecture
1989	BIOL 918	Physical Biochemistry	3	18	3 lecture
1989	PHCH 972	Mechanisms of Pharmaceutical Degradation	3	12	3 lecture
1989	PHCH 514	Pharmaceutics I	3	85	6 lecture
1989	PHCH 631	Pharmaceutics Lab II	1	85	52 laboratory

University of Colorado

1990	PHCH 870	Protein Structure and Stability	2	20	20 lecture
1990	PHCH 870	Protein Structure and Stability	2	20	20 lecture
1990	BIOL 922	Protein Biochemistry	3	10	4 lecture
1990	PHCH 624	Pharmaceutics II	3	85	9 lecture
1990	PHAR 3030	Pharmacy Calculations	1	100	7 lecture
1990	PHAR 3100/ 4100	Pharmaceutics I	3	200	14 lecture
1990	CHEM 6711	Advanced Topics in Biochemistry	4	25	3 lecture

VI. TEACHING ACTIVITY (CONTINUED)

YR.	COURSE		SEMESTER CREDITS	NO. OF STUDENTS	CONTACT HRS.
1991	PHSC 3110/ 4110	Pharmaceutics II	3	200	13 lecture
1991	PHSC 4110	Pharmaceutics Laboratory	1	80	76 laboratory
1991	PHAR 3030	Pharmacy Calculations	1	110	4 lecture
1991	PHAR 3100	Pharmaceutics I	3	110	13 lecture
1991	PHSC 3111	Pharmaceutics Laboratory	1	90	78 laboratory
1992	CHEM 5561	Physical Chemistry of Macromolecules	3	20	3 lecture
1992	PHSC 3110	Pharmaceutics II	3	110	14 lecture
1992	PHSC 3111	Pharmaceutics Laboratory	2	100	78 laboratory
1992	PHSC 3100	Pharmaceutics I	3	135	22 lecture
1993	PHSC 3110	Pharmaceutics II	3	130	22 lecture
1993	TXCL 7545	Principles of Drug Stability	1.3	2	10 lecture
1993	PHSC 3100	Pharmaceutics I	3	140	21 lecture
1993	PHSC 7656	Advanced Pharmaceutics	1.3	3	16 lecture
1993	PHSC 4810	Industrial Pharmacy	2	30	course coordinator
1994	PHSC 3110	Pharmaceutics II	3	140	45 lecture
1994	PHSC 3100	Pharmaceutics I	3	140	45 lecture
1994	PHSC 4810	Industrial Pharmacy	2	30	course coordinator
1994	PHSC 7480	Fundamentals of Drug Development and Drug Action	3.3	3	6 lecture

VI. TEACHING ACTIVITY (CONTINUED)

YR.	COURSE		SEMESTER CREDITS	NO. OF STUDENTS	CONTACT HRS.
1995	PHSC 3100	Pharmaceutics I	3	130	43 lecture
1995	PHSC 7300	Graduate Biochemistry	4	3	4 lecture
1995	MOLB 7800	Molecular Biology I	2.7	30	4 lecture
1995	PHSC 4810	Industrial Pharmacy	2	50	course coordinator
1995	PHSC 7370	Regulatory and Business Issues in Pharmaceutical Biotechnology	1.3	5	course coordinator
1996	PHSC 3110	Pharmaceutics II	3	130	1 lecture
1996	PHSC 3100	Pharmaceutics I	3	132	16 lecture/course coord.
1997	PHSC 3110	Pharmaceutics II	3	128	15 lecture
1997	PHSC 3100	Pharmaceutics I	3	105	24 lecture/course coord.
1997	PHSC 7300	Graduate Biochemistry	4	4	2 lecture
1997	PHSC 7350	Protein Chemistry	2.7	12	8 lecture/course coord.
1998	PHSC 3110	Pharmaceutics II	3	105	14 lecture
1998	PHSC 7370	Regulatory and Business Issues in Pharmaceutical Biotechnology	1.3	9	course coordinator
1998	PHSC 7354	Spectroscopic Analysis of Biomolecules	2.7	14	8 lecture/course coord.
1998	PHSC 3100	Pharmaceutics I	3	94	24 lecture/course coord.
1998	PHSC 7310	Graduate Pharmaceutics I	3	2	24 lecture/course coord.
1998/9	PHSC 7350	Protein Chemistry	2.7	5	8 lecture/course coord.
1999	PHSC 3110	Pharmaceutics II	3	90	14 lecture

VI. TEACHING ACTIVITY (CONTINUED)

YR.	COURSE		SEMESTER CREDITS	NO. OF STUDENTS	CONTACT HRS.
1999	PHRD 3600	Science Foundations I	3	90	22 lecture
1999	PHSC 7310	Graduate Pharmaceutics I	3	3	24 lecture/course coord.
1999	PHRD 3100	Pharmacy Seminar	2	90	2 lecture
1999	PHSC 7330	Issues in Drug Development	1.3	12	2 lecture
2000	PHSC 7345	Principles of Drug Delivery	1.3	8	4 lecture
2000	PHSC 7354	Spectroscopic Analysis of Biomolecules	2.7	13	6 lecture/course coord.
2000	PHRD 3600	Science Foundations I	3	90	12 lecture
2000	PHSC 7310	Graduate Pharmaceutics I	3	1	10 lecture/course coord.
2000	PHRD 3610	Science Foundations II	3	90	6 lecture
2000	PHRD 4700	Integrated Organ Systems III	3	90	2 lecture
2000	PHRD 3300	Experiential Practice I	1	90	6 laboratory
2000	PHSC 7330	Issues in Drug Development	1.3	13	4 lecture/course coord.
2000/1	PHSC 7350	Protein Chemistry I	2	20	17 lecture/course coord.
2001	PHRD 3600	Science Foundations I	3	115	12 lecture
2001	PHRD 5700	Integrated Organ Systems IX	3	85	2 lecture
2001	PHRD 4700	Integrated Organ Systems III	3	90	2 lecture
2001	PHRD 5200	Pharmacy Seminar	1	90	8 hours
2001	PRDO 5480	Pharmacy Seminar	1	60	8 hours
2001	PHRD 4100	Experiential Practice III	1	85	2 hours
2002	PHSC 7561	Introduction To Modern Biotechnology	1	15	1 hour

VI. TEACHING ACTIVITY (CONTINUED)

YR.	COURSE		SEMESTER CREDITS	NO. OF STUDENTS	CONTACT HRS.
2002	PHRD 5210	Pharmacy Seminar	1	90	8 hours
2002	PHSC 7370	Business Issues in Pharm. Biotechnology	1.3	12	6 lecture/course coord.
2002	PHRD 3600	Science Foundations I	3	120	13 lecture
2002	PHRD 3610	Science Foundations II	3	120	6 lecture
2002	PHRD 5700	Integrated Organ Systems IX	3	110	2 lecture
2002	PHSC 7330	Issues in Drug Development	1.3	12	2 lecture
2002/3	PHSC 7350	Protein Chemistry I	2	12	12 lecture

Other

Invited Lecturer, Center for Professional Advancement, Short Courses on "Stability of Protein Pharmaceuticals, Biologics, and Devices", New Brunswick, NJ, 1989-1993.

Invited Lecturer, Parenteral Drug Association Workshops on "Formulating Stable Biotechnology Products", New Brunswick, NJ, and San Diego, CA, 1995 and Lake Tahoe, CA 1996.

Invited Lecturer, Conference on Pharmaceutical Science and Technology Workshop on "Formulating Stable Protein Pharmaceutical Products", Chicago, IL, 1995 and 1996.

Invited Lecturer, American Association of Pharmaceutical Scientists, Short Course on "Issues in Formulation of Biopharmaceuticals", San Francisco, CA, 1998.

Invited Lecturer, American Association of Pharmaceutical Scientists, Short Course on "Lyophilization of Protein Pharmaceuticals", Indianapolis, IN, 2000.

Invited Lecturer, European Continuing Education College, Short Course on Formulation and Stabilization of Biomolecules", London, England, 2002.

Invited Lecturer, Formulation and Stabilization of Protein Pharmaceuticals, Breckenridge, CO, 2002

VII. ADVISING ACTIVITY

A. Thesis Advisor for Ph.D. Students

University of Kansas, Department of Pharmaceutical Chemistry

Ronda Gray (1988-1990, Ph.D. awarded, 1993)

Cecilia Oliyai (1988-1990, Ph.D. awarded, 1992) (joint with Dr. Ronald Borchardt)

Cynthia Stevenson (1988-1990, Ph.D. awarded, 1992) (joint with Dr. Ronald Borchardt)

University of Colorado, Department of Pharmaceutical Sciences

James Matsuura (1991-1996, Ph.D. awarded, 1996)

Robert Beauvais (1995-1999)

Jeffrey Meyer (1996-2001; Ph.D. awarded, 2001)

Charles Hughes (1996-2001; M.S. awarded, 2002)

Lixin Feng (1999-present) (joint with Dr. William Dernell, CSU)

Derrick Katayama (2000-present)

Mary Cromwell (2001-present)

ShuJun Bai (2002-present) (joint with Dr. John Carpenter)

Danny Chou (2002-present)

B. Member of Advisory Committee

University of Kansas, Department of Pharmaceutical Chemistry

Jay Sisco (1988-1989, Ph.D. awarded, 1989)

Shohba Arkalgud (1989, M.S. awarded, 1989)

Kaushik Dave (1989-1990, Ph.D. awarded, 1990)

University of Kansas, Department of Medicinal Chemistry

Sam Chou (1990)

University of Colorado, Department of Pharmaceutical Sciences

Gary Walega (1990-1991)

Scott Myers (1991-1992)

Daniel Womer (1993-1994, Ph.D. awarded, 1994)

Julie Derby (1993-1994)

S. Dean Allison (1993-1998, Ph.D. awarded, 1998)

Brent Kendrick (1994-1997, Ph.D. awarded, 1997)

LaToya Jones (1997-2001; Ph.D. awarded, 2001)

Tunde Adesunloye (1999-2001)

Yong-Sung Kim (1999-2002; Ph.D. awarded, 2002) (chair of the committee)

S. Krishnan (1999-2002; Ph.D. awarded, 2002) (chair of the committee)

Huiyu Zhou (1999-present)

Andy Kosky (2000-present) (chair of the committee)

Nancy Stolpman (2000-2002; Ph.D. awarded, 2002) (chair of the committee)

Susan Babuka (2001-2002) (chair of the committee)

Lorinda Girouard (2002-present)

Ye Zhang (2002-present)

Mayank Patel (2002-present)

University of Colorado, Department of Chemical Engineering

Richard Falk (1995-1998, Ph.D. awarded, 1998)
Serena Donnelly-Webb (1997-2001, Ph.D. awarded, 2001)
Jon Webb (1997-2000; Ph.D. awarded, 2000)
Jing Xu (1998-1999, M.S. awarded, 1999)
Danielle Biggs (1999-present)
Scott Lyman (1999-2000, M.S. awarded, 2000)
Richard St. John (2000-2001, Ph.D. awarded, 2001)
Roberto De Paz (2000-2001, Ph.D. awarded, 2001)
Eva Chi (2000-present)
Michael Stoner (2002-present)

C. Advisor for Postdoctoral Students

University of Colorado, Department of Pharmaceutical Sciences

Dr. Jen-Jen Lin (1998)
Dr. Chuan Li (1999)
Dr. Alexandra de Lille (2001-present) (joint with Dr. W. Dernell, CSU)

D. Host for Visiting Scientists

University of Colorado, Department of Pharmaceutical Sciences

Professor Lewis Stratton, Furman University (joint with John Carpenter)
Dr. Francesco Meriani, University of Trieste (joint with William Dernell)

VIII. ADMINISTRATIVE ACTIVITY AND UNIVERSITY SERVICE

School of Pharmacy, University of Kansas

Graduate Affairs Committee, 1988-1990

ad hoc Committee on Biotechnology in the Pharmacy Curriculum, 1989-1990

NMR Committee, 1989-1990

School of Pharmacy, University of Colorado

Student Ethics and Conduct Committee, 1990-1992, 1994-1999. Chair, 1997-1998

Curriculum Committee, 1990-1993. Served as Chair from 1992-1993

Executive Committee, Division of Pharmaceutical Sciences, 1991-1992

Computer and Information Sciences Committee, 1992-1993

Faculty Search Committees (8), 1991-2002. Served as Chair on two committees

Graduate Program in Pharmaceutical Sciences, Director, 1997-present

Computer and Information Technology Web Page Subcommittee, 1999

Scholastic Advancement and Appeals Committee, Chair, 2000-present

Appointment, Promotion, and Tenure Committee, 2000-2003

University of Colorado Health Sciences Center

Fitzsimons Research Park Advisory Committee, 1997-1999

Search Committee for Dean of the Graduate School, 1997-1998

Facilities and Administrative Waiver Committee, 2001-present

IX. SPECIAL ASSIGNMENTS

Chair, ad hoc Committee on Team Teaching Evaluations, School of Pharmacy, University of Colorado, 1992

Member, ad hoc Leadership and Planning Task Force, Division of Pharmaceutical Sciences, School of Pharmacy, 1993

Member, ad hoc Graduate Core Course Planning Committee, Department of Pharmaceutical Sciences, School of Pharmacy, 1993-1994

Member, ad hoc Committee on Remediation/Academic Assistance Process, School of Pharmacy, 1999

Member, State of Colorado Health Care Task Force Subcommittee on Mandated Health Care Costs, 1999

Member, Colorado Alliance for Bioengineering Executive Council, 2000-2001

X. HONORS

Visiting Summer Professor, Abbott Laboratories, 1989

Student (James Matsuura) won first place for best poster presentation at Graduate Research Association of Students in Pharmaceutics (GRASP) Meeting, Lincoln, NE, June, 1994

Invited Guest, Novo Nordisk Technology Conference on Protein Stability, Hvidøre, Denmark, August, 1997 (one of only five outside scientists invited)

1997 Research Achievement Award in Biotechnology from the American Association of Pharmaceutical Scientists

XI. PROFESSIONAL ACTIVITY AND PUBLIC SERVICE

A. Membership in Professional Organizations (past and present)

American Association for the Advancement of Science (AAAS)
American Association of Pharmaceutical Scientists (AAPS)
American Chemical Society (ACS)
American Phytopathological Society
Controlled Release Society
Biophysical Society
Protein Society

B. Grant Review Panels

National Science Foundation, Biophysics Section, ad hoc Reviewer (1990, 1991, 1997, 1998)
Parenteral Drug Association Foundation, Biotechnology Section (1992 and 1993)
North Carolina Biotechnology Center Seed Grants (1994)
Colorado Institute for Research in Biotechnology Seed Grants (1995-1999)
Israel Science Foundation, ad hoc reviewer, 2001
US Civilian Research and Development Foundation, ad hoc reviewer, 2002

C. Journal Referee

AAPS PharmSci
American Chemical Society Symposium Series
Archives of Biochemistry and Biophysics
Biochemistry
Biochimica et Biophysica Acta
Biophysical Journal
Bio/technology
Biotechnology and Bioengineering
Biotechnology Progress
Biopolymers
Chemico-Biological Interactions
Comparative Biochemistry and Physiology
Current Pharmaceutical Biotechnology
Encyclopedia of Human Biology
International Journal of Peptide and Protein Research
International Journal of Pharmaceutics
Journal of Agricultural and Food Chemistry
Journal of the American Chemical Society
Journal of Applied Polymer Science
Journal of Drug Targeting
Journal of Medicinal Chemistry
Journal of Organic Chemistry
Journal of Peptide Research
Journal of Pharmaceutical and Biomedical Analysis
Journal of Pharmaceutical Sciences

Life Sciences
Molecular Biology Reports
Nature Biotechnology
Peptide Research
Pharmaceutical Research
Protein Engineering
Protein Science
Separation Science

D. Editorial Boards

Editor, Journal of Pharmaceutical and Biomedical Analysis, 1999-2000
Member, Editorial Board, Journal of Pharmaceutical and Biomedical Analysis,
2000-2002.
Member, Editorial Board, Current Pharmaceutical Biotechnology, 1999-present

E. Other

Member, Organizing Committee, Rocky Mountain Biomedical Development
Forum, 1990-1993
Member, Awards Committee, Parenteral Drug Association, 1992
Chair, Abstract Screening Committee, BIOTEC Section, American Association of
Pharmaceutical Scientists (AAPS), 1992
Member, Advisory Board, Colorado Institute for Research in Biotechnology,
1993-present
Co-Chair (with John Carpenter), Organizing Committee, Colorado Protein
Stability Conference, 1994-present
Co-host, Visiting Professor, Dr. Lewis Stratton, Dept. of Biology, Furman
University, 1995-1996
Organizer, Colorado Perspectives on Drug Delivery Conference, meeting held in
July, 1996
Member, Program Committee, 1995 Conference on Pharmaceutical Science and
Technology in conjunction with the 1995 International Conference on
Food Science and Technology and the 26th Annual Meeting of the Fine
Particle Society, 1995
Member, Graduate Faculty, University of Colorado at Boulder, 1995-present
Member, Organizing Committee, Colorado Biopharmaceutical Drug Delivery
Conference, 1996-1997
Co-Director, University of Colorado Center for Pharmaceutical Biotechnology,
1997-present
Member, Program Committee, BIOTEC Section, American Association of
Pharmaceutical Scientists (AAPS), 1997-1998
Member, Program Committee, PDD Section, American Association of
Pharmaceutical Scientists (AAPS), 1997-1998
Member, Biomolecular Structure Program, University of Colorado Health
Sciences Center, 1997-1999
Member, Organizing Committee, Colorado Macromolecular Drug Delivery
Conference, 1998-present

**Member, Steering Committee, American Association of Pharmaceutical Scientists
(AAPS) Focus Group on Ocular Drug Delivery, 1999-2000**
**Member, Genomics/Biotechnology Exploratory Group, University of Colorado
Health Sciences Center, 1999**
Faculty Representative, Global Pharmaceutical Education Network, 2000-present

XII. INVITED SPEAKING ENGAGEMENTS

Local and State

YEAR	ORGANIZATION	TITLE
1988	University of Kansas Lawrence, KS	Circular Dichroism and Protein Structure
1989	Society for Applied Spectroscopy Kansas City Section Kansas City, MO	Studying the Structure of Proteins Using Circular Dichroism Spectroscopy
1990	University of Colorado School of Pharmacy Boulder, CO	Stability of Protein Pharmaceuticals
1990	Colorado State University Department of Biochemistry Fort Collins, CO	Stability of Protein Pharmaceuticals
1990	University of Colorado Molecular Biophysics Supergroup Boulder, CO	Stability of Protein Pharmaceuticals
1991	University of Denver Department of Chemistry Denver, CO	Stability of Protein Pharmaceuticals
1991	Colorado State University Fort Collins, CO	Career Opportunities in the Pharmaceutical Sciences
1995	University of Colorado School of Pharmacy Boulder, CO	Novel Methods for Stabilizing and Delivering Therapeutic Agents
1995	Colorado RNA Center Minisymposium, University of Colorado, Boulder, CO	Circular Dichroism Studies of Poly- nucleotides
1997	University of Denver Department of Chemistry Denver, CO	Hydrophobic Ion Pairing: The Power of a Simple Idea

1998	Colorado School of Mines Golden, CO	Hydrophobic Ion Pairing: The Power of a Simple Idea
1999	University of Colorado Department of Biology Colorado Springs, CO	Multidisciplinary Training in Pharmaceutical Biotechnology
1999	State of Colorado Legislature Health Care Task Force Denver, CO	The Future of Pharmaceutical Care
1999	University of Colorado HSC Health Services Grand Rounds Denver, CO	Biotechnology, Pharmaceutical Development, and Intellectual Property Issues
2001	University of Colorado Department of Biology Colorado Springs, CO	Hydrophobic Ion Pairing: The Power of a Simple Idea
2001	Univ. of Colorado HSC School of Medicine Div. of Medical Oncology Denver, CO	Controlled Delivery of Paclitaxel using an Aqueous Poloxamer Gel: Pharmaco- kinetics and Efficacy Studies
2001	Colorado State University Dept. of Chemistry Fort Collins, CO	Hydrophobic Ion Pairing: The Power of a Simple Idea
2002	Fitzsimons Fourteeners Aurora, CO	Introduction to HTD BioSystems

YEAR	ORGANIZATION	<u>National</u> TITLE
1988	Upjohn Company Kalamazoo, MI	Determination of Protein Structure Using Circular Dichroism Spectroscopy
1988	Eli Lilly Indianapolis, IN	Determination of Protein Structure Using Circular Dichroism Spectroscopy
1989	22nd Higuchi Research Conference Lake of the Ozarks, MO	Analyzing Protein Structure by Circular Dichroism Spectroscopy

1989	Abbott Laboratories N. Chicago, IL	Everything You Wanted to Know About Proteins
1990	Nasal and Pulmonary Delivery of Peptides and Proteins Princeton, NJ	Formulation Considerations: Solubility, Aggregation, and Chemical Degradation
1991	AAPS Eastern Regional Meeting East Brunswick, NJ	Spectroscopic Techniques for Determining Protein Structure
1991	Marion Merrill Dow Research Institute Kansas City, MO	Circular Dichroism Spectroscopy: Fundamentals, Techniques, and Applications
1993	Atrix Laboratories Fort Collins, CO	How Proteins Respond to Stress: Temperature and Solvent Effects
1993	AAPS Midwestern Regional Mtg. Chicago, IL	Spectroscopic Methods in the Analysis of Protein Stability
1993	Rocky Mountain Analytical Conference Denver, CO	Optical Spectroscopy in the Analysis of Protein Pharmaceuticals
1994	Somatogen, Inc. Boulder, CO	Current Research in Protein Structure and Stability at the Univ. of Colorado
1994	BioPharm National Meeting San Francisco, CA	Chemical and Physical Instabilities of Protein Pharmaceuticals
1994	Recovery of Biological Products VII San Diego, CA	Approaches for Increasing the Solution Stability of Proteins
1994	Biological Recognition at ONR Workshop Berkeley Springs, WV	Production of Soluble Enzymes in Organic Solvents Via Hydrophobic Ion Pairing
1994	Alza Corporation Palo Alto, CA	Potential for Hydrophobic Ion Pairing to Enhance Drug Delivery
1995	Cytel Corporation San Diego, CA	Structural Characterization of CY- 1899 Using FT-Infrared Spectroscopy
1995	Bayer Biotechnology Berkeley, CA	Aggregation and Precipitation in Protein Biopharmaceuticals

1995	AAPS Midwestern Regional Mtg Chicago, IL	Structure and Stability of Proteins in Nonaqueous Environments
1995	NeXstar Pharmaceuticals Boulder, CO	Novel Drug Delivery Methods
1996	Neurobiological Technologies, Inc. Richmond, CA	Stability and Structure of Peptides in Solution
1996	Ribozyme Pharmaceuticals, Inc. Boulder, CO	Novel Approaches for the Delivery of Therapeutic Biomolecules
1996	Bayer Biotechnology Berkeley, CA	Enhanced Delivery of Pharmaceuticals Using Ion Pairing and Supercritical Fluid Technology
1996	Trimeris, Inc. Durham, NC	Development of Polypeptide Drug Products
1996	Hoffman- LaRoche Nutley, NJ	Use of Integrated Approaches for Assessing Stability during Preformulation Studies of Protein Pharmaceuticals
1996	Bristol-Myers Squibb New Brunswick, NJ	Approaches for Altering Protein Solubility
1997	Millipore Corporation Bedford, MA	Physical and Chemical Instability of Proteins
1997	Bayer Corporation Clayton, NC	Chemical and Physical Instabilities in Protein Pharmaceuticals
1997	Centeon, Inc. Kankakee, IL	Solution and Lyophilized Formulations of Protein Pharmaceuticals
1997	Neurobiological Technologies, Inc. Richmond, CA	A Case Study in Peptide Aggregation: Solution Behavior of Human CRF
1997	Colorado Biopharmaceutical Delivery Conference Breckenridge, CO	Combining Hydrophobic Ion Pairing and Precipitation with a Compressed Antisolvent Technologies: An Alternative Method for Preparing Controlled Release Microsphere Dosage Forms

1998	2nd Symposium on the Analysis of Well Characterized Biotechnology Pharmaceuticals San Francisco, CA	Approaches to the Analysis of Protein Aggregation in Pharmaceutical Formulations
1998	Stability and Interactions of Proteins in Delivery Systems Workshop, Controlled Release Soc. Las Vegas, NV	Stability of Proteins and Peptides in Poloxamer Gels
1998	University of Kansas Lawrence, KS	Hydrophobic Ion Pairing: The Power of a Simple Idea
1998	G.D. Searle Skokie, IL	Protein Aggregation
1998	AAPS National Meeting San Francisco, CA	Conformational Stability of Protein Pharmaceuticals
1999	Amgen Thousand Oaks, CA	New Methods for Controlled Delivery of Biopharmaceuticals
1999	Alza Corporation Palo Alto, CA	Altering Protein Solubility: Are Protein Suspensions Possible Dosage Forms?
1999	32nd Higuchi Research Conference Lake of the Ozarks, MO	New Models for Graduate Education in the Pharmaceutical Sciences
1999	Elan Pharmaceuticals S. San Francisco, CA	Conformational Stability of Proteins: Living in Glass Houses
1999	IntraBiotics Pharmaceuticals Mountain View, CA	Chemical and Physical Stability of Protein Pharmaceuticals
1999	Novel Approaches for Stabilization of Biomaterials DARPA Workshop Breckenridge, CO	Chemical Instability of Proteins
1999	AAPS National Meeting New Orleans, LA	Nonaqueous Formulations of Proteins Via Hydrophobic Ion Pairing
2000	DARPA Meeting on Cell Stasis Washington, DC	Beyond Cell Biology: A Pharmaceutical Approach to Biopreservation

2000	Genentech, Inc. S. San Francisco, CA	High-Throughput Formulation: Meeting the Coming Challenge
2000	IDEC Del Mar, CA	Decoding the Sequences of Antibody Light Chains: The Power of Multivariate Statistical Analysis
2000	Covance Raleigh, NC	High-Throughput Development: Meeting the Coming Challenge
2000	Alza Corp. Palo Alto, CA	High-Throughput Development: Meeting the Coming Challenge
2000	Chiron Corp. Emeryville, CA	High-Throughput Development: Meeting the Coming Challenge
2000	ZymoGenetics Seattle, WA	High-Throughput Development: Meeting the Coming Challenge
2000	Immunex Corp. Seattle, WA	High-Throughput Development: Meeting the Coming Challenge
2000	AAPS National Meeting Indianapolis, IN	Practical Aspects of Lyophilization of Protein Pharmaceuticals
2001	Bayer Corp. Clayton, NC	Garbage In, Garbage Out: The Importance of Biophysical Characterization in Drug Development
2001	IBC Conference on Formulation of Biopharmaceuticals San Diego, CA	Garbage In, Garbage Out: The Importance Physicochemical Characterization in Drug Development
2001	Antigenics, Inc. Woburn, MA	High Throughput Drug Development: Meeting the Coming Challenge
2001	NaPro Biotherapeutics Boulder, CO	Controlled Delivery of Paclitaxel using an Aqueous Poloxamer Gel: Pharmacokinetic and Efficacy Studies
2002	National Park Service Workshop on Remote Delivery of Vaccines Fort Collins, CO	Controlled Release of Biomolecules

2002	6th Symposium on the Analysis of Well Characterized Biotechnology Pharmaceuticals Washington, DC	High Throughput Development of Proteins Pharmaceuticals
2002	Hope College Department of Chemistry Holland, MI	Hydrophobic Ion Pairing: The Power of a Simple Idea
2002	TSI St. Paul, MN	High Throughput Development: Innovation in Bioanalytics
2002	Alza Corporation Mountain View, CA	Stability and Solubility of Polypeptides
2002	Roche Pharmaceuticals Nutley, NJ	Stability and Solubility of Polypeptides

International

YEAR	ORGANIZATION	TITLE
1993	Fifth International Symposium on Circular Dichroism Pingree Park, Colorado, USA	Circular Dichroism of Peptides and Proteins in Nonaqueous Solvents
1994	Colorado Protein Stability Conf. Breckenridge, Colorado USA	Structure and Stability of Polypeptides Dissolved in Organic Solvents
1996	Imutec Corporation Scarborough, Ontario, CANADA	Use of NMR in the Analysis of Complex Biological Mixtures
1997	Novo Nordisk Technology Symposium on Protein Stability Hvidøre, DENMARK	Chemical Instability of Protein Pharmaceuticals: New Challenges
1997	Novo Nordisk Bagsveard, DENMARK	Chemical Instability of Protein Pharmaceuticals: New Challenges
1998	Colorado Protein Stability Conf. Breckenridge, Colorado USA	Effect of Additives on the Chemical Stability of Peptides and Proteins
2000	Colorado Protein Stability Conf. Breckenridge, Colorado USA	Decoding the Sequences of Antibody Light Chains: The Power of Multivariate Statistical Analysis

2000	Globalization of Pharmaceuticals Education Network Meeting Uppsala, SWEDEN	The Use of Biophysical Methods to Assess the Stability of Peptides and Proteins
2001	Bradford Particle Design Bradford, ENGLAND	Hydrophobic Ion Pairing: The Power of a Simple Idea
2001	University of Bradford Bradford, ENGLAND	High Throughput Development: Meeting the Coming Challenge
2002	Novartis Pharmaceuticals Basel, SWITZERLAND	Importance of Biophysical Characterization in Formulation of Protein Pharmaceuticals
2002	Conference on Drug Delivery of Cytokines Torino, ITALY	Structure and Stability of a Novel Interferon Intended for Oral Delivery
2002	Novartis Pharmaceuticals Basel, SWITZERLAND	Analysis of Proteins: Critical Techniques
2002	Novartis Pharmaceuticals Basel, SWITZERLAND	Chemical Stability of Proteins
2002	Novartis Pharmaceuticals Basel, SWITZERLAND	Preformulation and Formulation Strategies
2002	Novartis Pharmaceuticals Basel, SWITZERLAND	Development Strategies for High Dose Formulations of Antibodies
2002	Novartis Pharmaceuticals Basel, SWITZERLAND	Accelerated Stress testing in the Development of Protein Pharmaceuticals
2002	Serono Roma, ITALY	Projection to Latent Structures (PLS): Application to Pharmaceutical Development

XIII. GRANT/RESEARCH ACTIVITY

Proposals Funded:

SmithKline and French, Circular Dichroism Spectrophotometer Instrumentation Grant

Primary Investigator (P. I.), one-time grant, given in 12/88 for \$30,000.

This grant supported the renovation of a Cary 60 circular dichroism spectrophotometer which will provide an instrument capable of accurately measuring the far UV CD spectra of proteins and other biomolecules.

J.R. and Inez W. Jay Research Fund, The University of Kansas, Development of Peptide Agents for the Control of Trauma-Induced Inflammation Within the Cerebrovasculature

Co-P. I. with Dr. K. L. Audus and Dr. G. I. Georg, covering 7/89-6/90 for \$11,000 total costs.

This grant supported studies designed at synthesizing, characterizing, and testing vasopressin analogs which will be more stable and effective at controlling inflammation in the central nervous system.

Kansas University General Research Fund, Conformation-Activity Relationships in Calcitonin Gene-Related Peptide (CGRP)

P. I. of grant covering 7/88-6/89 for \$5,000 total costs.

This grant supported structural studies on CGRP. Once the conformation of CGRP in aqueous solution is determined, the importance of each structural element to activity and specificity will be evaluated.

Kansas University General Research Fund, Renaturation of Recombinant Protein Pharmaceuticals from Inclusion Bodies

P. I. of grant covering 7/89-6/90 for \$6,490 total costs.

This grant supported studies on the structural characterization of recombinant proteins found in inclusion bodies, as well as developing methods for increased efficiency in the solubilization and renaturation of these materials.

American Heart Association - Kansas Chapter, Design of Antagonists of Endothelin, a Potent Vasoconstrictor

P. I. of grant covering 6/89-5/90 for \$20,000 total costs.

This grant supported studies aimed at elucidating the three-dimensional structure of the peptide hormone, endothelin, and the subsequent design of antagonists as possible agents to control hypertension.

National Institutes of Health, Pharmaceutical Aspects of Biotechnology Training

Trainer of grant covering 12/89-11/94 for \$91,230 in direct costs (Year 1) (P. I. is Dr. Ronald T. Borchardt).

This training grant supported training of pre-doctoral students in various pharmaceutical aspects relating to biotechnology. Two of Dr. Manning's students were supported by this grant.

Abbott Laboratories, Thrombolytics Venture, Stability of Urokinase and Other Protein Thrombolytics

P. I. of grant covering 1/90-6/91 for \$19,071 total costs.

This grant supported studies on the thermal stability of thrombolytic proteins such as urokinase, prourokinase, and plasminogen. The role of solution conditions and additives in stabilization of these compounds will be evaluated.

Colorado Institute for Research in Biotechnology, Spectroscopic Methods for Assessing the Stability of Recombinant Protein Pharmaceuticals

P.I. of grant covering 7/90-6/91 for \$5,000 total costs.

This grant provided partial support for a circular dichroism (CD) spectrophotometer which would be used to analyze the stability of protein pharmaceutical conditions. These studies would provide insight into the proper formulation of these materials.

University of Colorado, Committee on Academic Planning and Programs, Assessing the Stability of Protein Pharmaceuticals by Circular Dichroism Spectroscopy

P.I. of grant covering 10/90-9/91 for \$5,345 costs.

This grant provided partial support for a circular dichroism (CD) spectrophotometer which would be used to analyze the stability of protein pharmaceutical conditions. These studies would provide insight into the proper formulation of these materials.

Takeda Abbott Laboratories, Pharmaceutical Product Development, Stability of Leuprolide Formulations

P.I. of grant covering 6/91-5/94 for \$45,000 total costs plus a supply budget of \$5,000 per year.

This grant supported studies on the mechanism of degradation, the development of stable formulations and sample analysis of dosage forms containing leuprolide, a LHRH agonist.

American Cyanamid, Starter Grant in Formulation Research

P.I. of grant covering 10/91-9/92 for \$5,000 total costs.

This grant supported work on the effect of excipients on the stability of protein and peptides.

Schering-Plough Pharmaceuticals, Carboxy-Terminal Sequencing of Proteins

Co-P.I. of grant covering 10/91-9/93 for \$20,000 total costs. (P.I. is E. Shefter)

This grant supported research on developing techniques to sequence the carboxy terminus of protein pharmaceuticals.

Atrix Laboratories, In Vitro/In Vivo Correlations for Release of Growth Factors from the Atrigel Delivery System

P.I. of grant covering 11/92-10/93 for \$48,000 total costs.

This grant supported the study of the relationship between release kinetics of growth factors from biodegradable polymers in vitro and in animals.

**University of Colorado Health Sciences Center, Office of the Chancellor,
Computing Resources Proposal**

Co-P.I. (with Jim Ruth of the School of Pharmacy) of grant covering 12/92-10/93 for \$35,000 total costs.

This grant provided needed computational resources for the School of Pharmacy's academic and administrative programs.

**Colorado Institute for Research in Biotechnology, Enhanced Delivery of Peptides
Via Hydrophobic Ion Pairing**

P.I. of grant covering 7/93-6/94 for \$15,000 total costs.

This grant supported work on evaluating the ability of hydrophobic ion pairing to improve the systemic delivery of peptide pharmaceuticals.

**Colorado Institute for Research in Biotechnology, Graduate Student Fellowship for
James Matsuura**

P.I. of grant covering 7/93-6/94 for \$7,500 total costs.

This grant supported James Matsuura as a student training in biotechnology.

**Office of Naval Research, Molecular Biology Program, Homogeneous Enzyme
Catalysis in Mixed Solvents**

P.I. of grant covering 10/94-9/95 for \$ 104,251 total costs.

This grant supports a project using hydrophobic ion pairing to affect the dissolution of active enzymes in nonaqueous solvents.

Cytel Corporation, Preliminary Studies on CY-1899

P.I. of grant covering 8/94-9/94 for \$800 total costs.

This grant was to make preliminary CD and IR measurements on CY-1899.

Scios Nova, Inc., Preliminary Studies on ANF-like Peptides

Co-P.I. (with John Carpenter of the School of Pharmacy) of grant covering 9/94-10/94 for \$1,250 total costs.

This grant was to make preliminary CD and IR measurements on an ANF derivative.

Cytel Corporation, Structural Basis for the Activity of CY-1899

Co-P.I. of grant (with John Carpenter of the School of Pharmacy) covering 11/94-5/95 for \$7,500 total costs and covering 6/95-12/95 for \$7,500 more in total costs.

This grant is to develop spectroscopic methods for assessing the structural basis of CY-1899 activity.

Tektagen, Inc., Structural Studies of Extracellular Receptors

P.I. of grant covering 5-95-8/95 for \$1,160 total costs.

This grant was to assess the solution structure extracellular receptors that might have therapeutic use.

Neurobiological Technologies, Inc., Structure and Activity of Human CRF

Co-P.I. of grant covering 2/95-6/95 for approximately \$4,000 total costs (John Carpenter is the P.I.).

This grant was to assess the solution structure and stability of CRF compounds that might have therapeutic use.

NeXstar Pharmaceuticals, Research Fellowships in the Pharmaceutical Sciences

P.I. of grant covering 1/95-6/95 for \$10,400 total costs and \$4,750 in total costs for 7/95-9/95.

These fellowships support undergraduate and graduate students in their research in pharmaceutical biotechnology.

AutoImmune, Inc., Stability of Soluble Type II Collagen

P.I. of grant covering 1/95-12/95 for approximately \$4,500 total costs.

This grant is to assess the thermal stability of soluble collagen for use in preventing disease.

NaPro Biotherapeutics, Use of Circular Dichroism Spectroscopy as an Analytical Method for Bioactive Compounds

P.I. of grant covering 1/95-12/95 for approximately \$1,000 total costs.

This grant supports investigations on the use of CD as an alternative to spectropolarimetry as a USP approved analytical method.

National Institutes of Health, α_1 -Proteinase Inhibitor Deficiency and Emphysema

Collaborator (along with John Carpenter) on grant covering 7/95-6/00 for \$232,109 (Year 1) total costs (Prof. Jerry Brown in the School of Medicine is the P.I.)

This grant supports studies on the structural aspects of α_1 -proteinase inhibitor and the impact on biological activity.

Imutec Corporation, In Vivo Anticancer Activity Studies of Virulizin

P.I. of grant covering 3/96-2/97 for \$75,425 total costs.

This grant would support ongoing efforts to better characterize Virulizin and determine its efficacy in treating lung cancer in mice (in collaboration with Prof. Al Malkinson).

NaPro Biotherapeutics, In Vivo Anticancer Studies of Taxol

P.I. of grant covering 3/96-2/97 for \$10,000 total costs.

This grant would support ongoing efforts to evaluate taxol for its efficacy in treating lung cancer in mice (in collaboration with Prof. Al Malkinson).

Neurobiological Technologies, Inc., Behavior of Human CRF in Aqueous Solution

P.I. of grant covering 4/96-3/00 for \$28,287 (\$22,450) total (direct) costs

This grant would support studies on the physical stability of human corticotropin releasing factor in aqueous solution.

Ribozyme Pharmaceuticals, Pharmacokinetic Studies of Selected Ribozymes

P.I. of grant covering 4/96-4/97 for approximately \$ 16,400 (\$13,106) total (direct) costs.

This grant would support collaborative studies on the ability of microspheres and gels to affect clearance rates in two animal models.

College of Veterinary Medicine and Biomedical Sciences, Colorado State University, In Vitro and In Vivo Evaluation of Gentamicin Impregnated Polylactic Acid Beads

Co-P.I. of grant covering 5/96-11/96 for \$14,500 total costs (P.I. is W. Dernell)

This grant would support studies examining the use of poly(lactide) beads for local delivery of aminoglycosides in the treatment of osteomyelitis.

Colorado RNA Center, Controlled Release of RNA from Polymeric Microspheres

Co-P.I. of grant (T. Randolph, P.I.) covering 7/96-6/97 for \$35,000 total costs.

This grant supports collaborative studies on the ability of microspheres and gels to affect clearance rates in two animal models.

Bayer Biotechnology, Role of Human Serum Albumin in Aggregation of Formulated Protein Pharmaceuticals

P.I. of grant covering 6/97-5/98 for \$50,000 total costs.

This grant will support studies on the role of HSA dimers as seeds for subsequent aggregation and precipitation of formulated proteins.

Colorado State University College of Veterinary Medicine and Biomedical Sciences, In Vivo Evaluation of Antibiotic Impregnated Beads in a Rat Osteomyelitis Model

Collaborator on grant covering 7/97-6/98 for \$12,000 direct costs (P.I. is W. Dernell, CSU)

This grant will support studies on the ability of biodegradable beads containing antibiotics to control osteomyelitis, either prophylactically or therapeutically.

RxKinetix, Inc., Controlled Release Drug Delivery Systems

P.I. of grant covering 4/98-3/03 approved for \$250,000 total costs. Actual paid was \$25,000.

This grant will support studies on novel drug delivery systems for antibiotics and anticancer compounds.

University of Colorado, Department of Pharmaceutical Sciences Seed Grant, Novel Cationic Detergents for Improved Delivery of DNA

Co-P.I. (with three other colleagues) for grant covering 5/97-4/98 for \$10,000 total costs.

This grant supports studies on the development of new materials for preparation of cationic liposome delivery systems for DNA.

Bayer Plasma Fractionation, Stability of Human Serum Albumin during Processing

P.I. of grant covering 6/97-5/98 for \$46,380 total costs.

This grant will support studies on the stability of HSA during processing stresses.

Colorado RNA Center, Controlled Release of RNA from Polymeric Microspheres

Co-P.I. of grant (T. Randolph, P.I.) covering 7/97-6/98 for \$25,000 total costs.

This grant supports collaborative studies on the ability of injectable microsphere formulations to control release of ribozymes in vivo.

Alza Research Institute, Support of the Colorado Biopharmaceutical Delivery Conference

Co-P.I. of grant (J. Carpenter, P.I.) covering the 1997 and 1999 meetings for \$50,000 total costs.

This grant will support the drug delivery conference hosted by the University of Colorado Biopharmaceutical Delivery Conference.

Colorado RNA Center, Controlled Release Microspheres for Delivery of Ribozyme Pharmaceuticals

Co-P.I. of grant covering 7/98-6/99 for \$25,000 total costs.

Colorado Institute for Research in Biotechnology, Graduate Student Fellowship

Fellowship was given to Jeffrey Meyer for 1998-1999 (\$8,000 total award)

Colorado Institute for Research in Biotechnology, A Controlled Release Drug Delivery System for the Treatment of Breast Cancer

P.I. of grant covering 7/98-6/99 for \$17,500 total costs.

This grant supports research on the use of intracavitary drug delivery systems for immunotherapy in a breast cancer model.

Baxter Hyland, Analysis of Monoclonal Antibodies

P.I. of grant covering 3/98-5/98 for \$ 8,400 in total costs.

This contract supported studies on the solution behavior of therapeutic antibodies.

National Institutes of Health, Training in Pharmacology of Antineoplastic Agents

Preceptor (P.I. is A. Kraft) for 12/98-11/03 for 778,261 (833,571) direct (total) costs

This grant will support postdoctoral trainees in cancer research. Mentor of one trainee (Dr. A. De Lille) who is supported from 7/01-6/02.

Elan Pharmaceuticals, Biophysical Characterization of Neuropeptides

P.I. of grant covering 11/98-6/01 for \$51,200 in total costs.

This grant supports studies on the physical state of neuropeptide pharmaceuticals.

National Institutes of Health, Aerosol-Based Nanoparticle Drug Delivery System for Tuberculosis

Collaborator (Lawrence Ng, P.I.) of grant covering 4/99-3/03 for \$920,000 total costs

This grants supports work on the development of inhaled controlled release treatments for TB.

Bayer Corporation, Stability of Interleukin-4 Analogs

P.I. of grant covering 1/99-12/99 for \$42,000 total costs.

This grant supports work on the stability of IL-4-like compounds in solution and the solid state.

Coulter/Corixa Pharmaceuticals, Characterization of Protein Pharmaceuticals

P.I. of grant covering 9/98-10/01 for \$17,000 total costs.

This grant supports work on the structural stability of protein pharmaceuticals.

Genzyme Pharmaceuticals, Pilot Study on the Use of Hyaluronates as Delivery Systems for Proteins

P.I. of grant covering 7/99-1/00 for \$3,000 total costs.

This grant supports work on the use of hyaluronates to stabilize proteins in gel-based drug delivery systems.

American Foundation for Pharmaceutical Education, Graduate Fellowship to Jeffrey Meyer

Fellowship was given to Jeffrey Meyer for 1999-2000 (\$8,000 total award). Renewed for 2000-2001 (\$6,000).

G.D. Searle, Stabilization of Lyophilized Protein Pharmaceuticals

P.I. of grant covering 12/99-11/00 for \$45,000 total costs.

This grant supports work on the stability of protein pharmaceuticals in the solid state.

National Institutes of Health, Leadership Training in Pharmaceutical Biotechnology

Co-P.I. (T. Randolph, PI) of training grant covering 7/01—6/06 for \$1,000,000 total costs.

This grant provides graduate student support for the Center's training programs.

Colorado Institute for Research in Biotechnology, Controlled Release Drug Delivery System for Cancer Therapy

Co-P.I. (W. Dernell, PI) of grant covering 7/90-6/00 for \$12,000 total costs.

This grant supports research on the use of intracavitary drug delivery systems for immunotherapy in a breast cancer model.

Bayer Corporation, Development of High Throughput Formulation Strategies

P.I. of grant supporting sabbatical work covering 12/99-11/00 for \$40,000.

This grant supported travel and research into new methods for improving the efficiency of the formulations process for biopharmaceuticals.

McKee Foundation, Pharmacology Laboratory Equipment

P.I. (along with W. Dernell) of gift for \$45,000 in total costs.

This gift will support establishing a pharmacology laboratory in the new Animal Cancer Center at Colorado State University.

National Science Foundation, Shared Instrumentation Grant CTS 0079612

Collaborator (T. Randolph, P.I.) on grant covering 9/00-8/01 for \$192,000.

This grant will provide a number of instruments dedicated to solid state characterization of biomaterials.

HTD Biosystems, Studies on New Interferon Products

P.I. of contract covering 3/01-4/02 for \$40,000 total costs.

This contract supported studies on the stability and solubility of a novel interferon.

GonexPets, Preformulation of Toxin-Gonadotropin Conjugate

P.I. of grant covering 8/01-7/02 for \$45,000 total costs.

This grant covers studies on the stability and structure of a toxin-gonadotropin conjugate.

Human Genome Sciences, Solution Behavior of a Novel Protein Hormone

P.I. of grant covering 1/02-12/02 for \$55,000 total costs.

This grant supports studies on the structure and stability of growth factors in the solid state.

ICOS, Kinetics of Protein Aggregation

P.I. of grant covering 5/02-4/03 for \$60,000 total costs.

This grant supports studies on the appearance of protein aggregates during storage.

HTD Biosystems, Studies on New Interferon Products

P.I. of contract covering 5/02-4/03 for \$15,000 total costs.

This contract supported studies on the stability and solubility of a novel interferon.

HTD Biosystems, Studies on Pegylated Proteins

P.I. of contract covering 4/02-3/03 for \$15,000 total costs.

This contract supported studies on the stability and solubility of a novel interferon.

Colorado State University, Head of Pharmacology Laboratory, ACC

P.I. of contract to provide 20% of my salary from 12/02-11/04.

Submitted:

NIH, LC/MS/MS Purchase

Co-investigator (R. Hodges, P.I.) of grant covering 10/03-9/04 for \$284,315 in total costs.

This grant will support the purchase of a micro-scale HPLC system and mass spectrometer.

NIH, Affect of Preservatives on Protein Stability

Co-P.I. (J. Carpenter, P.I.) of grant covering 8/03-7/08 for \$1,000,000 in direct costs.

This grant would support biophysical studies on the impact of preservatives on protein aggregation.

NIH, Development of a Stable Botulism Vaccine

Project Leader (I. Henderson, P.I.) of a U01 contract covering 7/03-6/07 for \$1.1 million in direct costs.

XIV. PUBLICATIONS

A. Refereed Journals

"Reduction of Metal Carbonyl Compounds Using Alkali Metal Carbides", Mark C. Manning and William C. Trogler, *Inorg. Chim. Acta* **1981**, 50, 247-250.

"X α Calculations and Spectroscopic Studies of Triruthenium and Triosmium Dodecacarbonyl", Bernard Delley, Mark C. Manning, Donald E. Ellis, Joseph Berkowitz, and William C. Trogler, *Inorg. Chem.* **1982**, 21, 2247-2253.

"Electronic Absorption Spectra of Tetra- μ -acetatodimolybdenum in Low Temperature Matrices" Mark C. Manning and William C. Trogler, *Inorg. Chem.* **1982**, 21, 2797-2800.

"The Electronic Structure of V(CO)₆. Why It Is Black", Gary F. Holland, Mark C. Manning, Donald E. Ellis, and William C. Trogler, *J. Am. Chem. Soc.* **1983**, 105, 2308-2314.

"Electronic Absorption and Emission Spectra of Complexes Containing Dichromium, Dimolybdenum, and Ditungsten Quadruple Bonds", Mark C. Manning and William C. Trogler, *J. Am. Chem. Soc.* **1983**, 105, 5311-5320.

"Spectroscopic and Theoretical Studies on Binuclear Molybdenum (II) Carboxylates", Mark C. Manning, Gary F. Holland, Donald E. Ellis, and William C. Trogler, *J. Phys. Chem.* **1983**, 87, 3083-3088.

"Molecular Orbital Calculations on the Oligopeptides Netropsin, Distamycin, and Related Compounds", Mark C. Manning and Robert W. Woody, *Biopolymers* **1986**, 25, 2065-2082.

"Theoretical Determination of the Circular Dichroism of Proteins Containing Closely-Packed Antiparallel β Sheets", Mark C. Manning and Robert W. Woody, *Biopolymers* **1987**, 26, 1731-1752.

"Preparation and Characterization of Palladium(II)- and Platinum(II)-OTeF₅ Complexes", Mark R. Colman, Mark C. Manning, Oren P. Anderson, and Steven H. Strauss, *Inorg. Chem.* **1987**, 26, 3958-3960.

"Synthesis and Reactions of Dinuclear Palladium Complexes Containing Methyls and Hydride on Adjacent Palladium Centers: Reductive Elimination and Carbonylation Reactions", S.J. Young, B. Kellenberger, Joseph H. Reibenspies, S.E. Himmel, M. Manning, O.P. Anderson, and J.K. Stille, *J. Am. Chem. Soc.* **1988**, 110, 5744-5753.

"Circular Dichroism Studies of Distorted α Helices, Twisted β Sheets, and β Turns", Mark C. Manning, Mali Illangasekare, and Robert W. Woody, *Biophys. Chem.* **1988**, 31, 77-86.

"Comparison of the Secondary Structures of Human Class I and Class II MHC Antigens by IR and CD Spectroscopy", Joan C. Gorga, Aichun Dong, Mark C. Manning, Robert W. Woody, Winslow S. Caughey, and Jack L. Strominger, *Proc. Natl. Acad. Sci. USA* **1989**, 86, 2321-2325.

"Contribution of Aromatic Side Chains to the Circular Dichroism of Basic Bovine Pancreatic Trypsin Inhibitor (BPTI): A Theoretical Study", Mark C. Manning and Robert W. Woody, *Biochemistry* **1989**, 28, 8609-8613.

"Theoretical CD Calculations of Polypeptide Helices. Determination of the Important Electronic and Geometric Factors", Mark C. Manning and Robert W. Woody, *Biopolymers* **1991**, 31, 569-586.

Published as a faculty member :

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"Evaluation of Cisplatin in Combination with a Biologic Response Modifier in a Rodent Mammary Carcinoma Model", E. Morello, W.S. Dernell, C.A. Kuntz, A. Nelson, M.C. Manning, N. Ehrhart, M. Lafferty, and S.J. Withrow, Veterinary Cancer Society Meeting, Chicago, IL, December, 1997.

"Solution Behavior of Human Corticotropin Releasing Factor", Jeffrey D. Meyer, Bert Ho, and Mark C. Manning, Annual Student Research Forum, University of Colorado Health Sciences Center, Denver, CO, January, 1998.

"The DNA Packaging Enzyme of Phage λ : Dimerization and Oligomerization of the Small Subunit May Involve a Hydrophobic Interface and Intermolecular Disulfide Bond", J.D. Meyer, A. Hanagan, M.C. Manning, and C.E. Catalano, 42nd Biophysical Society Annual Meeting, Poster M-Pos168, Kansas City, MO, February, 1998, *Biophys. J.* **1998**, 74, A72.

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"Comparative Infrared and CD Spectroscopic Analysis of α_1 -Protease Inhibitor and Ovalbumin", A. Dong, J.D. Meyer, M.C. Manning, J. Brown, and J.F. Carpenter, 42nd Biophysical Society Annual Meeting, Poster W-Pos127, Kansas City, MO, February, 1998, *Biophys. J.* **1998**, 74, A277.

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"In Vitro and In Vivo Evaluation of Gentamicin-Impregnated Polylactic Acid Beads", W.S. Dernell, J.D. Meyer, R.F. Falk, R.M. Kelly, J.E. Shively, D.J. Kroll, T.W. Randolph, M.C. Manning, C.A. Kuntz, R. Dewell, B.E. Powers, S.J. Withrow, and F.B. Garry, 44th Annual Meeting of the Orthopaedic Research Society, New Orleans, LA, March, 1998.

"Solution Behavior of Human Corticotropin Releasing Factor", Jeffrey D. Meyer, Bert Ho, and Mark C. Manning, Pharmaceutics Graduate Student Research Meeting, Lawrence, KS, June, 1998.

"Hydrophobic Ion Pairing (HIP) of Compounds Containing a Single Positive Charge. The Effect of Solution Conditions on Ion-Paired Complex Formation", Jessica Sterna, Susan J. Manning, Emily Evans, Jeffrey D. Meyer, Eli Shefter, Theodore W. Randolph, Gerald L. Yewey, and Mark C. Manning, Merck Undergraduate Research Seminar, Estes Park, CO, June, 1998.

"Detection of Structural Changes in Nucleotide-Based Therapeutics using Circular Dichroism Spectroscopy", Sambou S. Jatta, Robert M. Beauvais, Thomas J. Anchordoquy, and Mark C. Manning, Merck Undergraduate Research Seminar, Estes Park, CO, June, 1998.

"Cos-7 Transfection with Polyamidoamine Dendrimers: A Comparative Study", Robert Serravo, Bin Tain, Mark Manning, David Kroll, Tom Anchordoquy, and Lawrence Ng, Merck Undergraduate Research Seminar, Estes Park, CO, June, 1998.

"Comparative FT-IR and CD Spectroscopic Analysis of α_1 -Proteinase Inhibitor and Ovalbumin", Aichun Dong, Jeffrey D. Meyer, Jerry L. Brown, Mark C. Manning, and John F. Carpenter, Colorado Protein Stability Conference, Breckenridge, CO, July, 1998.

"In vivo Evaluation of Antibiotic-Impregnated Beads in a Rat Osteomyelitis Model", W.S. Dernell, S.J. Withrow, C.A. Kuntz, M. Lafferty, B.E. Powers, M.C. Manning, J.E. Shively, J.D. Meyer, R.F. Falk, and T.W. Randolph, Eleventh Annual Colorado Biotechnology Symposium, Fort Collins, CO, September, 1998.

"Evaluation of Intracavitary Slow Release Paclitaxel Chemotherapy in a Rodent Model of Breast Cancer", V.S. Bregazzi, W.S. Dernell, D.J. Huber, S.J. Withrow, G.K. Ogilvie, M. Manning, B.E. Powers, R. Schochet, and M. Lafferty, 18th Annual Meeting of the Veterinary Cancer Society, Estes Park, CO, October, 1998.

"Assessment of DNA Structure within Non-Viral Delivery Systems by Fourier Transform Infrared Spectroscopy", T. Anchordoquy, S.D. Allison, J.-J. Lin, M.C. Manning, and J.F. Carpenter, Abstract 2500, AAPS National Meeting, San Francisco, CA, November 1998, *PharmSci* 1998, 1, S-281.

"Structural Characterization of Human Growth Hormone Subjected to Zinc-Induced Precipitation", Tzung-Hong Yang, Jeffrey L. Cleland, Theodore W. Randolph, Mark C. Manning, and John F. Carpenter, Abstract 3614, AAPS National Meeting, San Francisco, CA, November 1998, *PharmSci* **1998**, 1, S-536.

"Aggregation of Human Serum Albumin during Bioprocessing", Jen-Jen Lin, Jeffrey D. Meyer, John F. Carpenter, and Mark C. Manning, Abstract 21, Western Regional AAPS Meeting, San Diego, CA, April, 1999.

"Biophysical and Biochemical Characterization of a DNA Binding Domain of gpNu1, a Phage λ Packaging Protein", Q. Yang, T. de Beer, J. Baran, M.C. Manning, M. Overduin, and C.E. Catalano, Poster M-Pos140, Biophysical Society Meeting, Baltimore, MD, February, 1999, *Biophys. J.* **1999**, 76, A177.

"Sample Processing Concerns for Solid Proteins in FTIR Spectroscopy", Jeffrey D. Meyer, Mark C. Manning, and John F. Carpenter, Poster PS 16, 31st Pharmaceutics Graduate Student Research Meeting, Kansas City, KS, June, 1999.

"Effect of Crystallinity on Activation of Alveolar Macrophage Cells by Poly(L-lactide) and Poly(lactide-co-glycolide) Microparticles", D.L. Biggs, C.S. Lengsfeld, L.K. Ng, M. Manning, and T. Randolph, Colorado Macromolecular Drug Delivery Conference, Breckenridge, CO, July, 1999.

"Comparison of Effects of a Non-specific Stabilizing Solute and a Specific Ligand on Conformational Dynamics of Ribonuclease A and S", Y.-S. Kim, B.S. Chang, B.S. Kendrick, T.W. Randolph, M. Manning, and J.F. Carpenter, Colorado Macromolecular Drug Delivery Conference, Breckenridge, CO, July, 1999.

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"Sample Processing Concerns for Solid Proteins in FTIR Spectroscopy", Jeffrey D. Meyer, Mark C. Manning, and John F. Carpenter, Poster 11, Twelfth Annual Colorado Biotechnology Symposium, Boulder, CO, September, 1999.

"Effect of Poly(L-lactide) Microparticle Crystallinity on Macrophage Inflammatory Response", Danielle L. Biggs, Corrine S. Lengsfeld, Theodore W. Randolph, L.K. Ng, and Mark Manning, Poster 45, Twelfth Annual Colorado Biotechnology Symposium, Boulder, CO, September, 1999.

"Comparison of Effects of a Non-specific Stabilizing Solute and a Specific Ligand on Conformational Dynamics of Ribonuclease A and S", Yong-Sung Kim, Mark Manning, John F. Carpenter, Byeong S. Chang, Brent S. Kendrick, and Theodore W. Randolph, Poster 53, Twelfth Annual Colorado Biotechnology Symposium, Boulder, CO, September, 1999.

"In Vivo Evaluation of Antibiotic-Impregnated Beads in a Rat Osteomyelitis Model", W.S. Dernell, S.J. Withrow, M.C. Manning, C.A. Kuntz, M. Lafferty, B.E. Powers, J.E. Shively, R.F. Falk, J.D. Meyer, and T.W. Randolph, American College of Veterinary Surgeons National Meeting, San Francisco, CA, September, 1999.

"Effect of Poly(l-lactide) Microparticle Crystallinity on Alveolar Macrophage Inflammatory Response", Danielle Biggs, Corinne Lengsfeld, Mark C. Manning, Ka-yun Ng, and Theodore Randolph, 29th Annual Biochemical Engineering Symposium, Norman, OK, October, 1999.

"Sucrose Induces More Restricted Conformational Fluctuations of Ribonuclease A and S and Cytochrome c", Y.S. Kim, L.S. Jones, A. Dong, B.S. Chang, M.C. Manning, and J.F. Carpenter, Poster 3726, AAPS National Meeting, New Orleans, LA, November, 1999, *PharmSci* 1999, 1, S-2465.

"Aggregation of Human Serum Albumin during Bioprocessing", J.J. Lin, J.D. Meyer, J.F. Carpenter, and M.C. Manning, Poster 3452, AAPS National Meeting, New Orleans, LA, November, 1999, *PharmSci* 1999, 1, S-2172.

"Irreversible Protein Aggregation under Physiological Conditions: Characterization and Thermodynamic Inhibition", S. Krishnan, E. Chi, J. Webb, B.S. Chang, M.C. Manning, T.W. Randolph and J.F. Carpenter, FASEB Summer Research Conference: Amyloids and Other Protein Misfolding Diseases", Copper Mountain, CO, June, 2000.

"Counteracting Effects of Renal Solutes on Amyloid Fibril Formation by Immunoglobulin Light Chains", Yong-Sung Kim, Stephen P. Cape, Eva Chi, Rosemarie Raffin, Priscilla W. Stevens, Fred J. Stevens, Alan Solomon, Mark C. Manning, Theodore W. Randolph, and John F. Carpenter, FASEB Summer Research Conference: Amyloids and Other Protein Misfolding Diseases", Copper Mountain, CO, June, 2000.

"Counteracting Effects of Renal Solutes on Amyloid Fibril Formation by Immunoglobulin Light Chains", Yong-sung Kim, Stephen P. Cape, Eva Chi, Rosemarie Raffin, Priscilla W. Stevens, Fred J. Stevens, Alan Solomon, Mark C. Manning, Theodore W. Randolph, and John F. Carpenter, Colorado Protein Stability Conference, Breckenridge, CO, July, 2000.

"Precipitation of a Model Protein by Hyaluronic Acid and Its Derivatives", Lixin Feng, Derrick S. Katayama, and Mark C. Manning, Colorado Protein Stability Conference, Breckenridge, CO, July, 2000.

"Irreversible Protein Aggregation under Physiological Conditions: Thermodynamic Inhibition and Characterization", Sampathkumar Krishnan, Eva Chi, Jonathon Webb, Byeong S. Chang, Mark C. Manning, Theodore W. Randolph, and John F. Carpenter, Colorado Protein Stability Conference, Breckenridge, CO, July, 2000.

"Structural Control of Methionine Oxidation in Human Corticotropin Releasing Factor" Jeffrey D. Meyer, Bert Ho, and Mark C. Manning, Colorado Protein Stability Conference, Breckenridge, CO, July, 2000.

"Vertebral Osteomyelitis in a Bottlenose Dolphin, *Tursiops truncatus*: A Novel Treatment using Sustained Release, Antibiotic-Impregnated, Biodegradable Microspheres", Caroline E.C. Goertz, J. Lawrence Dunn, Mark C. Manning, Theodore W. Randolph, Derrick Katayama, Danielle Biggs, Rod Cole, Adam Brockman, Johnny Cardinnes, and David J. St. Rubin, American Association of Zoo Veterinarians and International Aquatic Animal Medicine Joint Annual Conference, New Orleans, LA, September, 2000.

"Effect of Poly(L-lactide) Microparticle Crystallinity on Alveolar Macrophage Activation" Danielle Biggs, Theodore W. Randolph, Ka-yun Ng, Brooks Hybertson, and Mark C. Manning, Thirteenth Annual Colorado Biotechnology Symposium, Fort Collins, CO, September, 2000.

"Counteracting Effects of Renal Solutes on Amyloid Fibril Formation by Immunoglobulin Light Chains", Yong-sung Kim, Mark C. Manning, John F. Carpenter, Stephen P. Cape, Eva Chi, Theodore W. Randolph, Rosemarie Raffin, Priscilla W. Stevens, Fred J. Stevens, and Alan Solomon, Thirteenth Annual Colorado Biotechnology Symposium, Fort Collins, CO, September, 2000.

"Systemic Paclitaxel Delivery using a Poloxamer-Based Aqueous Suspension: A Pharmacokinetic Study", Lixin Feng, Charles L. Hughes, William S. Dernell, Mark W. Duncan, and Mark C. Manning, Poster 3524, AAPS National Meeting, Indianapolis, IN, November, 2000.

"Ion Pairing of Therapeutic Agents using a Prodrug Approach: Study of Isoniazid Sulfonate", Huiyu Zhou, David J. Claffey, James A. Ruth, Ka-yun Ng, Theodore W. Randolph, and Mark C. Manning, Poster 2525, AAPS National Meeting, Indianapolis, IN, November, 2000.

"Enhanced Potency of Ion-Paired Complexes of Cis-platin and Tetracycline", Lixin Feng, Danielle L. Biggs, Derrick S. Katayama, Ka-yun Ng, William S. Dernell, Theodore W. Randolph, and Mark C. Manning, Poster 3304, AAPS National Meeting, Indianapolis, IN, November, 2000.

"Effect of Poly(l-lactide) Microparticle Crystallinity on Alveolar Macrophage Activation", Danielle L. Biggs, Corinne S. Lengsfeld, Brooks M. Hyberston, Ka-yun Ng, Mark C. Manning, and Theodore W. Randolph, Poster 2123, AAPS National Meeting, Indianapolis, IN, November, 2000.

"Effects of Sample Processing on Lyophilized Proteins Analyzed by Infrared Spectroscopy", Jeffrey D. Meyer, John F. Carpenter, and Mark C. Manning, Poster 2388, AAPS National Meeting, Indianapolis, IN, November, 2000.

"Structural Control of Methionine Oxidation in Human Corticotropin Releasing Factor", Jeffrey D. Meyer, Bert Ho, and Mark C. Manning, Poster 2275, AAPS National Meeting, Indianapolis, IN, November, 2000.

"Irreversible Protein Aggregation under Physiological Conditions: Characterization and Thermodynamic Inhibition", S. Krishnan, E. Chi, J. Webb, B.S. Chang, M.C. Manning, T.W. Randolph and J.F. Carpenter, Colorado Alliance for Bioengineering Day at Fitzsimons, Aurora, CO, December, 2000.

"Counteracting Effects of Renal Solutes on Amyloid Fibril Formation by Immunoglobulin Light Chains", Yong-Sung Kim, Stephen P. Cape, Eva Chi, Rosemarie Raffin, Priscilla W. Stevens, Fred J. Stevens, Alan Solomon, Mark C. Manning, Theodore W. Randolph, and John F. Carpenter, Colorado Alliance for Bioengineering Day at Fitzsimons, Aurora, CO, December, 2000.

"Enhanced Efficacy of Ion-Paired Tetracycline" D. Biggs, C. Lengsfeld, M. Manning, and T. Randolph, Controlled Release Society Annual Meeting, San Diego, CA, June, 2001.

"Cellular Response to Poly(L-Lactide) Microparticles for Pulmonary Delivery", D. Biggs, C. Lengsfeld, B. Hybertson, L.K. Ng, M. Manning, and T. Randolph, Controlled Release Society Annual Meeting, San Diego, CA, June, 2001.

"Polymeric Microspheres in Gene Delivery: A DNA Release and Polymer Degradation Study", Mayank M. Patel, Thomas J. Anchordoquy, Theodore W. Randolph, and Mark C. Manning, Colorado Macromolecular Drug Delivery Conference, Breckenridge, CO, July, 2001.

"Cellular Response to Poly(L-Lactide) Microparticles for Pulmonary Delivery", Danielle L. Biggs, Corinne S. Lengsfeld, Brooks M. Hybertson, Lawrence K. Ng, Mark C. Manning, and Theodore W. Randolph, Colorado Macromolecular Drug Delivery Conference, Breckenridge, CO, July, 2001.

"Release Kinetics of Isoniazid Methanesulfonate from Poly(L-Lactide) Microspheres Produced by Precipitation with a Compressed Antisolvent", Huiyu Zhou, Danielle L. Biggs, David J. Claffey, James A. Ruth, Theodore W. Randolph, Lawrence K. Ng, and Mark C. Manning, Colorado Macromolecular Drug Delivery Conference, Breckenridge, CO, July, 2001.

"In Vitro and In Vivo Assessment of a Hydrophobic Ion Paired (HIP) Complex of Vancomycin", Lixin Feng, Derrick Katayama, Vicki J. Jameson, J. Shively, William S. Dernell, Theodore W. Randolph, and Mark C. Manning, Colorado Macromolecular Drug Delivery Conference, Breckenridge, CO, July, 2001.

“Cellular Response to Poly(L-Lactide) Microparticles for Pulmonary Delivery”, Danielle L. Biggs, Brooks Hybertson, Corinne S. Lengsfeld, Ka-yun L. Ng, Mark C. Manning, and Theodore W. Randolph, Poster T3515, AAPS National Meeting, Denver, CO, October, 2001.

“A Microtiter Plate-Based Assay of Protein Solubility: Measurements with Less Material and Less Time”, Derrick S. Katayama and Mark C. Manning, Poster R5257, AAPS National Meeting, Denver, CO, October, 2001.

“In Vitro and In Vivo Assessment of a Hydrophobic Ion Paired (HIP) Complex of Vancomycin”, Lixin Feng, Derrick Katayama, Jesse Shively, Theodore W. Randolph, William S. Dernell, and Mark C. Manning, Poster T3761, AAPS National Meeting, Denver, CO, October, 2001.

“High Throughput Formulation: Nonisothermal Stress Testing of Biopharmaceuticals”, L. Steve Mitchell, Derrick Katayama, Rajiv Nayar, and Mark C. Manning, Poster M2371, AAPS National Meeting, Denver, CO, October, 2001.

“Localized Delivery of Paclitaxel Using an Aqueous Poloxamer Gel: An Efficacy Study”, Lixin Feng, William S. Dernell, Vicki J. Jameson, and Mark C. Manning, Poster W4327, AAPS National Meeting, Denver, CO, October, 2001.

“Characterization of Lipid-DNA Interactions by Fluorescence Resonance Energy Transfer, Anisotropy, and Circular Dichroism”, Ye Zhang, William Garzon-Rodriguez, Mark C. Manning, and Thomas J. Anchordoquy, Poster M 2354, AAPS National Meeting, Denver, CO, October, 2001.

“Aggregation of Human Serum Albumin under Different Stresses: Effect of Pressure and Non-Specific Solutes”, Sampathkumar Krishnan, Richard S. St. John, Mark C. Manning, Theodore W. Randolph, and John F. Carpenter, Poster M2362, AAPS National Meeting, Denver, CO, October, 2001.

“A Mechanistic Study of Benzyl Alcohol-Induced Aggregation of a Predominantly Beta-Sheet Model Protein”, LaToya S. Jones, Byeong S. Chang, Mark C. Manning, Theodore W. Randolph, and John F. Carpenter, Poster M2297, AAPS National Meeting, Denver, CO, October, 2001.

“Characterization and Thermodynamic Inhibition of Aggregation of Granulocyte Colony Stimulating Factor under Physiological Conditions”, Sampathkumar Krishnan, Eva Y. Chi, Jonathan S. Webb, Byeong S. Chang, Mark C. Manning, Theodore W. Randolph, and John F. Carpenter, Poster M2349, AAPS National Meeting, Denver, CO, October, 2001.

"Combinations of Bulking Agents and Sucrose in the Lyophilization of a Monoclonal Antibody: A Computer-Aided Design of Experiment Study" Jeffrey D. Meyer, Rajiv Nayar, John F. Carpenter, and Mark C. Manning, Poster M2204, AAPS National Meeting, Denver, CO, October, 2001.

"Release Kinetics of Isoniazid Methanesulfonate from Poly(L-Lactide) Microspheres Produced by Precipitation with a Compressed Antisolvent", Huiyu Zhou, Danielle L. Biggs, Theodore W. Randolph, Ka-yun Ng, and Mark C. Manning, Poster T 3367, AAPS National Meeting, Denver, CO, October, 2001.

"Polymeric Microspheres in Gene Delivery: A DNA Release and Polymer Degradation Study", Mayank M. Patel, Thomas J. Anchordoquy, Theodore W. Randolph, and Mark C. Manning, Poster W4758, AAPS National Meeting, Denver, CO, October, 2001.

"Enhanced Efficacy of Ion-Paired Tetracycline", Danielle L. Biggs, Corinne S. Lengsfeld, Mark C. Manning, and Theodore W. Randolph, Poster W4759, AAPS National Meeting, Denver, CO, October, 2001.

"Suitability of Electrostatic Spraying for Macromolecular Therapeutics", C.S. Lengsfeld, Y. Lentz, T. Anchordoquy, D. Dunn-Rankin, and M.C. Manning, ILASS Americas, 15th Annual Conference on Liquid Atomization and Spray Systems, Madison, WI, May, 2002.

"Retrospective Statistical Analysis of Lyophilized Protein Formulations of Progenipoietin Using PLS. Determination of the Critical Parameters for Long-Term Storage Stability", Derrick S. Katayama, Carol F. Kirchhoff, Carrie M. Elliott, Robert Johnson, Jeffry Borgmeyer, Barrett R. Thiele, David L. Zeng, Hong Qi, John D. Ludwig, and Mark C. Manning, Colorado Protein Stability Conference, Breckenridge, CO, July, 2002.

"Stability of Human Serum Albumin in Solution under Different Stresses: Kinetics, Thermodynamics and Structural Transitions", Sampathkumar Krishnan, K. Sudhinra Rao, Rick St. John, Theodore W. Randolph, Mark C. Manning, and John F. Carpenter, Colorado Protein Stability Conference, Breckenridge, CO, July, 2002.

"Thermodynamics of Congo Red Binding to an Amyloidogenic Protein and Its Effects on Amyloid Fibril Formation of the Protein", Yong-sung Kim, Theodore W. Randolph, Fred J. Stevens, Mark C. Manning, and John F. Carpenter, Colorado Protein Stability Conference, Breckenridge, CO, July, 2002.

"Application of Near Infrared Spectroscopy to Measuring the Crystallinity of Glycine in Freeze-Dried Samples", Shujun Bai, Rajiv Nayar, John F. Carpenter, and Mark C. Manning, Colorado Protein Stability Conference, Breckenridge, CO, July, 2002.

"Applications of Gas-Phase Electrophoretic Mobility Molecular Analysis (GEMMA) in the Study of Protein Stability and Aggregation", Danny K.C. Chou, Theodore W. Randolph, and Mark C. Manning, Colorado Protein Stability Conference, Breckenridge, CO, July, 2002.

"Incorporation of Isoniazid into Poly(L-Lactide) Microspheres using a Prodrug Approach", Huiyu Zhou, Danielle L. Biggs, Daniel Jarmer, David J. Claffey, James A. Ruth, Theodore W. Randolph, Ka-yun Ng, and Mark C. Manning, Global Pharmaceutical Education Network Meeting, Ann Arbor, November, 2002.

"Development of Oral Formulations of a Novel Cytokine", Derrick S. Katayama, Lorelie Villarete, Danny Chou, Rajiv Nayar, and Mark C. Manning, Global Pharmaceutical Education Network Meeting, Ann Arbor, MI, November, 2002.

G. Patent Applications:

Work done as a faculty member :

"Ion-Pairing of Drugs for Improved Efficacy and Delivery", Eli Shefter and Mark C. Manning, patent application 07/961,162 filed October 14, 1992. PCT Int. Pat. Appl. WO 94 08577. Abandoned and incorporated into applications listed below.

"Method for Producing Ultrafine Pharmaceutical Powders Using a Compressed Gas Antisolvent", Theodore W. Randolph, Mark C. Manning, Eli Shefter and Richard F. Falk, patent disclosure filed with the University of Colorado in September, 1994. Combined with the application above as "Solubilization of Hydrophilic Pharmaceutical Substances in an Organic Solvent and Preparation of Pharmaceutical Powders Using the Same". The United States patent application was filed on June 7, 1995 and foreign applications were filed as well. The US patent (5,770,559) was issued on June 23, 1998. A second US patent (5,981,474) was issued on November 9, 1999.

"Controlled Release Drug Delivery System for the Treatment of Inner Ear Disorders", Michael J. Hart, Mark C. Manning, R. Michael Kelly, Jeffrey D. Meyer, James Matsuura, and Eli Shefter, patent disclosure filed with the University of Colorado in May, 1995. The University decided to pursue a patent application as of August, 1995. A provisional patent application. No. 60015572, was filed with the United States Patent and Trademark Office on April 18, 1996. Full U.S. and PCT patent applications (WO9738698A1) were filed on April 18, 1997 listing Eli Shefter, Mark C. Manning, and Michael Hart as inventors.

"Temperature Sensitive Gels for Sustained Delivery of Protein Drugs", Lewis P. Stratton, John F. Carpenter, and Mark C. Manning, patent disclosure filed with the University of Colorado in September, 1995. A United States patent application, number 08/679,199 was filed on July 12, 1996. A US patent (5,861,174) was issued on January 19, 1999. A

divisional application was filed on January 15, 1999. A European patent application (EP910342A1) was filed on March 15, 1999.

"Biocompatible Cationic Detergents and Uses Therefor", Eli Shefter, James A. Ruth, Jeffrey D. Meyer, Mark C. Manning, David J. Kroll, and David J. Claffey, patent disclosure filed with the University of Colorado in January, 1996. A provisional United States patent application was filed on September 13, 1996. Full U.S. and PCT patent applications (WO9810649A1) were filed on October 29, 1996.

"Biodegradable Antibiotic Beads for Treatment of Osteomyelitis", Mark C. Manning, Theodore W. Randolph, Richard F. Falk III, Jeffrey D. Meyer, Stephen J. Withrow, and William J. Dernell, patent disclosure filed with the University of Colorado, January, 1996.

"Improved Formulations of Oral Antibiotics for Administration to Animals and Humans", Mark C. Manning, Jeffrey D. Meyer, Richard F. Falk III, Theodore W. Randolph, James E. Matsuura, Eli Shefter, and Ryan R. Manning, patent disclosure filed with the University of Colorado, January, 1996.

NOTE: An exclusive license for all of the above intellectual property was assigned to RxKinetix, Inc. by the University of Colorado, March, 1997.

"Sustained Release Composition Including Amorphous Polymer", Theodore W. Randolph, Richard Falk, and Mark Manning, patent disclosure 8045 filed with the University of Colorado, November, 1997. A provisional U.S. patent, 60/078,390, entitled, "Sustained-Release Composition Including Amorphous Polymer", was filed in March, 1998. A PCT application (WO9947543A2) was filed in March, 1999. A US patent application (09/403,412) was filed on March 8, 2000. A continuation was filed on June 7, 2001.

"Controlled Release of Ribozymes from Biodegradable Microspheres", Mark C. Manning, Theodore W. Randolph, Robert Beauvais, Richard Falk, and Mark Reynolds, patent disclosure filed with the University of Colorado, November, 1997. The intellectual property was assigned to Ribozyme Pharmaceuticals, Inc., Boulder, CO in March, 1998.

"Metal-Assisted Hydrophobic Ion Pairing", Jeffrey D. Meyer and Mark C. Manning, patent disclosure filed with the University of Colorado, April, 1998.

"Controlled Release of Anticancer Drugs from a Thermosensitive Gel", Mark C. Manning, William S. Dernell, Victoria Bregazzi, and Stephen J. Withrow, patent disclosure filed with the University of Colorado, September, 1998. A provisional patent was filed in November, 1999.

"Hydrophobic Ion Paired Drug Complexes for Controlled Release and Tunable Potency", Douglas Pitera, Corinne Lengsfeld, Mark Manning, and Ted Randolph, patent disclosure filed with the University of Colorado, October, 1999. A provisional patent was filed in November, 1999.

"Novel Drug Delivery System for Treatment of Local Infections", Mark C. Manning, Derrick Katayama, Douglas Pitera, Corinne Lengsfeld, and Theodore W. Randolph, patent disclosure filed with the University of Colorado, April, 2000. A provisional patent was filed in September, 2000.

"Increased Potency of Antibiotics and Anticancer Compounds via Ion Pairing" Mark C. Manning, William S. Dernell, Theodore W. Randolph, Lixin Feng, Danielle S. Biggs, and Derrick Katayama, patent disclosure filed with the University of Colorado, May, 2000. A US patent application (09/717,486) was filed on November 20, 2000, entitled "Compositions and Methods for Administering Chemotherapeutic Agents".

"Stabilization of Nebulized Solutions of Tissue Plasminogen Activator", Derrick Katayama, Mark C. Manning, John Repine, and Kathleen S. Stringer, patent disclosure filed, September, 2002. A provisional patent application is to be filed in October, 2002.